REMARKS

Claims 48-57, 60-71, 77 and 78 remain under consideration in this application. No claim has been allowed

Claim Rejection - 35 USC § 112, First Paragraph

Claims 48-57, 60-71 and 77-78 remain rejected under 35 USC § 112, first paragraph as failing to comply with the enablement requirement for the reasons set forth in the earlier Action of September 12, 2008 and because, in the Examiner's opinion, the applicants have not provided any persuasive arguments or objective evidence showing predictable, positive *in vitro - in vivo* correlation for the claimed molecules. This rejection is respectfully traversed.

The applicants cannot agree with the Examiner's position that the published documents support the unpredictable nature of any *in vivo/in vitro* correlation. The Examiner has supported this position by reference to general comments in those documents that *in vivo* delivery of DNA-based molecules can be difficult due to: poor cellular uptake by endocytosis; inability of the DNA-based molecule to exit the endosome-liposome compartment; and inability of the DNA-based molecule to enter the nucleus.

Experimental Evidence

The applicants submit that those general comments are not applicable to the present invention. As discussed below, we

disagree with the Examiner's characterization of the cited documents and submit that they are generally positive about DNA-based therapeutic agents. Furthermore, the present inventors have evidence (both in the application and, further, in the enclosed accompanying experimental data contained in Exhibits A and B, attached hereto) demonstrating that the claimed molecules are capable of entering cells, exiting endosome-liposome vesicles and reaching the nucleus where they can have a therapeutic effect *in vivo*.

The applicants, however, would like to point out what they believe to be a more accurate interpretation of the documents which the Examiner cites in support of the rejection.

Opalinska *et al.*

Contrary to the Examiner's allegations, Opalinska *et al.* is seen as generally positive about the progress and prospects made using nucleic-acid-based drugs.

For example, on page 504 (left-hand column), Opalinska *et al.* comment that oligonucleotides have been successfully used for: "blocking transcription and inducing specific mutations, both *in vitro* and *in vivo*". Furthermore, page 508 of that document contains the results of 15 clinical trials using nucleic-acid-based drugs.

Patil *et al.*

Patil *et al.* is similarly positive about oligonucleotide-

based therapies, and essentially reiterates the points in Opalinska et al.

For example, on page E62, Patil *et al.* report numerous clinical trials for DNA-based therapeutics. In addition, the right-hand column of that page states that: "the use of DNA delivery systems has not only improved the pharmacokinetics of DNA-based therapeutics but has also achieved efficient targeted introduction of these molecules into desired tissues."

Accordingly, applicants submit that there is, in fact, adequate *in vivo/in vitro* correlation to show that the claimed invention is clearly enabled and meets the requirements of 35 USC § 112, first paragraph. The Examiner is therefore respectfully requested to take into account the above and reconsider and withdraw the present rejection.

Claim Rejection - 35 USC § 102

Claims 48, 51-54, 62-64 and 67-68 remain rejected under 35 USC § 102(a) as being anticipated by Lewis et al (Bioconjugate Chemistry, 2002, 13:1176-1180). This rejection is again respectfully traversed.

Lewis et al. does not disclose a method as defined in Claims 48-70, 77 and 78, which involves a molecule that binds to a site at or associated with a selected apoptosis-related gene which site is present in the cell genome.

Conversely, it is clear that Lewis *et al.* does relate to

the use of an antisense molecule that binds to mRNA (see, for example, lines 9-12 of the abstract). Thus, the molecule in Lewis *et al.* does not bind to a site present on the cellular genome, as required by the claimed method.

Since the molecule in Lewis *et al.* is different from the molecule used in the presently claimed method, we consider that Claim 72 (which relates to a pharmaceutical composition comprising that molecule) is novel for at least the same reasons.

It is also noted that claims 48-50, 52-53, 55-56, 62-63 and 67-68 remain rejected under 35 USC § 102(e) as being anticipated by Buluwela et al (WO 03/010308 A2). Claims 48-56, 59, 62-63 and 67-68 remain rejected under 35 USC § 103 as being anticipated by Hart et al (WO 03/033701 A1). Both of these rejections are respectfully traversed.

Both WO 03/010308 and WO 03/033701 relate, generally, to methods for modulating gene expression.

There is no disclosure in either document of the regulation of an apoptosis-related gene, or the induction or repression of apoptosis in a cell. Accordingly, the method as defined in Claims 48-70, 77 and 78 is novel over either document.

Claim Rejection - 35 USC § 103

It is further noted that claims 48-57, 60-65 and 67-68 have again been rejected under 35 USC § 103(a) as being unpatentable

over Wolffe et al (WO 02/26960 A2) in view of Reed (USPN 5,831,066) and Li et al (Genes & Development, 2002, 16:687-692). This rejection is also respectfully traversed.

WO 02/26960 (Wolffe *et al.*)

WO 02/26960 relates to several methods, one of which relates to the modulation of gene expression. However, it is clear that, in every embodiment relating to gene expression in WO 02/26960, the molecule used in that document is a fusion molecule comprising a zinc finger protein as the DNA-binding domain (see, for example, page 4, lines 18 to page 6, line 6 and page 10, lines 3 to 10, of WO 02/26960).

Thus, none of the molecules used in WO 02/26960 comprise a DNA-binding domain which is an oligonucleotide, as required by the present claims.

For example, in the embodiment on page 5, lines 1 to 7, the fusion molecule comprises a DNA-binding domain, a localisation domain and a regulatory domain; however, that fusion molecule comprises a zinc finger protein as its DNA-binding domain, not an oligonucleotide as defined in the present claims.

It would not be obvious to a skilled person to replace the zinc finger protein DNA-binding domain of the WO 02/26960 molecule to arrive at the presently claimed invention. Throughout the description of the "modulating gene expression" method of WO 02/26960, it is made clear that zinc finger

proteins are versatile binding domains, and the skilled person would understand that zinc finger proteins are therefore advantageous in that method.

For example, page 19, lines 5 to 7, make it clear that zinc finger proteins are capable of binding a range of target molecules (*i.e.* DNA, RNA and/or protein) and can be engineered to bind to predetermined sequences (see page 19, lines 19 to 29, explain that zinc finger proteins). Furthermore, zinc finger proteins are said to be capable of binding DNA that is packaged in nucleosomes and chromatin (see page 30, lines 21-26). No such advantages or features of any other possible binding domains are discussed in WO 02/26960 or recognised by the authors of that document.

Thus, in WO 02/26960, zinc finger proteins were purposely selected for their perceived advantages. That teaching would be appreciated by the skilled person and would not be abandoned; accordingly, the claimed method is not obvious.

Moreover, for the sake of argument, even if the Examiner considers that the claimed fusion molecule would have been developed, the presently claimed method would still not have been obvious.

WO 02/26960 speculates that the expression of "*bcl-2*" and "apoptotic factors" could be modulated. However, those disclosures are no more than an indication that those genes

could be investigated as possible targets for modulation; there is no indication that modulating those genes could be performed in a particular way to achieve an overall cellular effect, such as promoting apoptosis. Accordingly, a skilled person would not be motivated to develop the claimed method and, even if he did, have no expectation that such a method would be successful. For example, WO 02/26960 does not contain any evidence or experimental data to indicate that any genes could be modulated sufficiently using that method to promote apoptosis.

In the absence of such a teaching or suggestion, the skilled person would be highly skeptical that the WO 02/26960 method could promote apoptosis. At the time WO 02/26960 was published, several methods purporting to promote apoptosis had already been described, but were known not to be capable of actually inducing cell death in a reproducible and consistent manner (see, for example, page 4, lines 1 to 6, of the present application).

Conversely, the claimed method and fusion molecules are capable of promoting apoptosis. The Examples of the application clearly demonstrate that the claimed fusion molecules specifically down-regulate expression of Bcl-2 (see, for example, Figures 2 and 3).

During prosecution of the corresponding European patent application, we submitted additional experimental data

(enclosed) to further demonstrate that the claimed method and fusion molecules are capable of down-regulating Bcl-2 to a level that promotes apoptosis in cancer cells, and does so in a manner equivalent to (or better than) existing antisense-based molecules known to promote apoptosis.

Li *et al.*

Li *et al.* is a scientific journal article relating to the assembly of histone deacetylase complexes, and their role in transcriptional repression.

Li *et al.* teaches that the Mad1 protein only recruits certain co-factors involved in gene suppression (see, for example, page 691, left-hand column, final paragraph).

Thus, a skilled person reading Li *et al.* would not consider Mad1 to be a good candidate molecule for use in a method for suppressing gene expression. From the teaching of Li *et al.*, the skilled person would not expect Mad1 to be capable of fully modulating gene expression of any gene.

US 5,831,066 (Reed *et al.*)

US 5,831,066 relates to a method of regulating *Bcl-2* gene expression. However, a skilled person reading that document would consider that modulating *Bcl-2* expression would not necessarily induce apoptosis.

In particular, it is clear that the method of US 5,831,066 modulates *Bcl-2* gene expression solely to render cells sensitive

to an administered chemotherapeutic agent, and that it is that agent that induces apoptosis (see, for example, column 3, lines 18-26). Accordingly, the skilled person reading US 5,831,066 would consider that modulating *Bcl-2* expression is not sufficient alone to induce apoptosis.

As discussed above, before the priority date of the present application, it was known that it was difficult to induce cellular apoptosis and several methods purporting to promote apoptosis were known not to be capable of actually inducing cell death in a reproducible and consistent manner (see, for example, page 4, lines 1 to 6, of the present application). Conversely, as demonstrated in the present application (and the enclosed additional experimental data), the presently claimed method is capable of inducing apoptosis.

Accordingly, we believe that US 5,831,066 actually teaches away from the present invention in which modulating the expression of an apoptosis gene alone can be used to induce apoptosis.

Given the above amendments, taken together with the remarks herein, applicants are convinced that the present claims should be allowable over the cited references, taken either singularly or in combination, and reconsideration and allowance of the claims is respectfully requested.

Respectfully submitted,

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